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Systolic and diastolic hypertension among patients on hemodialysis: Musings on volume overload, arterial stiffness and erythropoietin

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Abstract

Hypertension among patients on hemodialysis is predominantly systolic (either isolated or combined with diastolic hypertension), whereas the scenario of isolated diastolic hypertension is rare and more common in younger patients. Uncontrolled hypertension that persists despite aggressive antihypertensive drug therapy is a reflection of the volume overload that is a prominent mediator of systolic and diastolic BP elevation. Clinical-trial evidence supports the notion that dry-weight probing is an effective strategy to improve BP control, even when overt clinical signs and symptoms of volume overload are not present. Accelerated arterial stiffness influences the patterns and rhythms of interdialytic ambulatory BP and is a major determinant of isolated systolic hypertension in hemodialysis. Post-hoc analyses of the Hypertension in Hemodialysis patients treated with Atenolol or Lisinopril (HDPAL) trial, however, suggest that arterial stiffness does not make hypertension more resistant to therapy and is unable to predict the treatment-induced improvement in left ventricular hypertrophy. A combined strategy of sodium restriction, dry-weight adjustment and antihypertensive medication use was effective in improving ambulatory BP control regardless of the severity of underlying arteriosclerosis in HDPAL. Other non-volume-dependent mechanisms, such as erythropoietin use, appear to be also important contributors and should be taken into consideration, particularly in younger hemodialysis patients with diastolic hypertension. In this article, we explore the role of volume overload, arterial stiffness and erythropoietin use as causes of systolic versus diastolic hypertension in patients on hemodialysis. We conclude with clinical practice recommendations and with a call for a “volume-first” approach when managing hemodialysis hypertension.

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arterial stiffness; erythropoietin use; hemodialysis; hypertension; volume overload

Epidemiology

Hypertension among patients on hemodialysis is highly prevalent, difficult to diagnose and often remains poorly controlled.[1] In sharp contrast to the linear association of blood pressure (BP) with clinical outcomes in non-dialysis populations, most of the observational data among those on hemodialysis show a U-shaped or J-shaped relationship of dialysis-unit BP with mortality.[2–4] These observations have raised concerns on whether controlling high BP is a beneficial therapeutic approach of hypertensive hemodialysis patients.

That said, the observations supporting the concept of "reverse" epidemiology of hypertension in hemodialysis are contrasted by studies showing that elevated BP recorded either with home or with ambulatory BP monitoring provides a direct mortality risk signal.[5–7] Analyses of outcome data from incident hemodialysis patients participating in the Chronic Renal Insufficiency Cohort (CRIC) study also show that, unlike the inverse prognostic association of dialysis-unit BP, out-of-dialysis-unit BP — recorded during a prespecified follow-up CRIC visit and not with home or ambulatory BP monitoring — exhibits a linear relationship with the risk of cardiovascular morbidity[8] and all-cause mortality.[9]

These diverse and somewhat contradictory prognostic associations are likely explained by the excessive variability of pre- and postdialysis BP recordings and their poor diagnostic performance in detecting the actual BP burden recorded via out-of-dialysis BP monitoring.[10,11]

The most common phenotype of BP elevation among patients on hemodialysis is that of systolic hypertension, whereas isolated diastolic hypertension is rare and occurs predominantly in younger patients. This particular phenotype contrasts with the distribution of systolic and diastolic BP in the general population and reflects the acceleration of the arteriosclerotic process and premature vascular ageing in patients with end-stage kidney disease on hemodialysis. In a cross-sectional analysis of 2,535 clinically stable hemodialysis patients participating in a multi-centre trial, the prevalence of hypertension (defined as 1-week average predialysis BP >150/85 mmHg or current use of antihypertensive drugs) was 86%.[12] Although 88% of hypertensives were being treated with antihypertensive drugs, only 30% of them had adequate control of their BP. Among those with drug-treated but uncontrolled BP, 88% had systolic hypertension, either alone (35%) or combined with diastolic hypertension (53%), whereas only 12% had isolated diastolic hypertension.[12] In the age-group of <30 years, the prevalence of isolated diastolic hypertension was as high as 29%.[12]

Studies using the "gold-standard" method of ambulatory BP monitoring provide, perhaps, more precise estimates of the distribution of systolic versus diastolic hypertension. Among 70 hemodialysis patients participating in a diagnostic-test study, 24% had ambulatory BP

within the normotensive range, 37% had isolated systolic hypertension and 36% had combined systolic/diastolic hypertension; isolated diastolic hypertension was detected in only 3% of participants.[13] In a larger cohort of 105 hemodialysis patients, normotension or adequately controlled ambulatory BP was detected in 63% and ambulatory hypertension was present in 37% of participants.[14] Once again, systolic hypertension (isolated or combined with diastolic hypertension) was more common than isolated diastolic hypertension (33% vs. 3%, respectively).[14]

In the following sections of this article, we explore the contribution of volume overload, arterial stiffness and other non-volume-dependent mechanisms in pathogenesis of systolic and diastolic hypertension among patients on hemodialysis. We conclude with clinical practice recommendations for the assessment and management of hypertension in this high-risk population (Figure 1).

Volume overload

The most rigorous study to support the notion that hypertension in hemodialysis is a manifestation of volume expansion is the Dry-Weight Reduction in Hypertensive Hemodialysis Patients (DRIP) trial.[15] In DRIP, 150 hypertensive hemodialysis patients without overt symptoms of volume expansion were randomly assigned in a 2:1 ratio to ultrafiltration or control groups for 8 weeks. In the ultrafiltration group, all participants had their dry-weight probed until the occurrence of symptoms indicating that their dry-weight was achieved. In the control group, participants had only physician visits without any modification in their prespecified dry-weight.[15]

Study participants were receiving stable background therapy with a mean number of 2.7 antihypertensive drugs; nevertheless dry-weight reduction of 0.9 kg between the baseline and week 4 provoked a placebo-subtracted change of −6.9 mmHg [95% confidence interval (CI): −12.4 to −1.3 mmHg] in 44-hour ambulatory systolic BP and a change of −3.1 mmHg (95% CI: −6.2 to −0.02 mmHg) in diastolic BP.[15] Ambulatory BP reduction in response to dry-weight probing was sustained over the 8-week-long follow-up of the trial. In the control group, absence of any intervention in dry-weight was associated with the development of accelerated hypertension (defined as 44-hour ambulatory BP ≥175/105 mmHg) in 5 out of 50 participants. In the DRIP trial, the benefit of BP-lowering with probing of dry-weight was seen regardless of presence or absence of pitting pedal edema. This clinical-trial evidence established that volume overload is a cause of systolic and diastolic hypertension among patients on hemodialysis.[15]

A secondary analysis of the DRIP trial showed that dry-weight reduction causes alterations in the patterns and rhythms of interdialytic BP.[16] The chronobiology of BP among patients on hemodialysis is markedly altered and is characterized by a steady rise in BP during the interdialytic interval.[17] The rate of BP change appears to be proportional to the interdialytic weight gain.[17] Furthermore, BP in the majority of hemodialysis patients follows a blunted circadian amplitude due to the sleep and wake cycle, a phenomenon described as “non-dipping”.[18]

Using a trended cosinor model, analysis of 35,302 measurements obtained by 400 interdialytic ambulatory BP recordings in 145 DRIP participants showed that augmented volume withdrawal therapy in those assigned to the ultrafiltration group lowered the average systolic and diastolic BP (intercept) but increased the rate of BP rise (slope) over the interdialytic interval at week 4 and week 8 of follow-up.[16] No changes in the intercept BP and slope pattern were evident during follow-up in those assigned to the control group. Dry-weight reduction had no effect on the amplitude of systolic and diastolic BP variation and was unable to restore the nocturnal dipping pattern. Accordingly, the chronobiological "signature" of volume overload on interdialytic BP is characterized by an elevated intercept but blunted slope pattern.[16]

The evidence provided by the DRIP trial has important implications in the management of hemodialysis hypertension in daily clinical practice. Firstly, management of dry-weight should not rely on the presence or absence of clinical signs and symptoms of volume excess.[1] Although patients with clinically overt volume overload were not eligible in DRIP, probing of dry-weight was a strategy that culminated in a clinically meaningful reduction of ~7/3 mmHg in 44-hour ambulatory BP over the 8-week-long course of the trial.[15]

It is worth noting that pedal edema is a poor marker of volume status. A cross-sectional analysis of 146 asymptomatic hemodialysis patents found that while pedal edema was associated with several cardiovascular risk factors such as age, body mass index, left ventricular (LV) mass, it did not reflect the volume status as measured using inferior vena cava (IVC) diameter, blood volume monitoring and other plasma volume markers such as B-type natriuretic peptide.[19] An observation that was similarly contrary to clinical wisdom was reported in 79 clinically stable hemodialysis patients in the ongoing Lung Water by Ultra-Sound Guided Treatment to Prevent Death and Cardiovascular Complications in High Risk ESRD Patients with Cardiomyopathy Trial (LUST). They found that lung crackles, either alone or combined with pedal edema, were unreliable evidence of the severity of lung congestion as assessed objectively with the lung ultrasound B line score.[20]

Initiation or intensification of antihypertensive drug therapy to control high BP without adequate management of dry-weight is an approach that is likely to fail.[1] DRIP participants at baseline had uncontrolled BP, confirmed by 44-hour ambulatory BP monitoring, despite the concurrent use of 2.7 antihypertensive agents. The factor mediating the inadequate BP control was the presence of sub-clinical volume expansion.[15] Similarly, in a cross-sectional study of 369 hemodialysis patients, the prevalence of hypertension (defined as 44-hour ambulatory BP ≥135/85 mmHg or current use of antihypertensive medications) was 82%.[21] Although 89% of hypertensive patients were being treated with antihypertensive drugs, ambulatory BP was adequately controlled in only 38%. In multivariate regression analysis, the use of more antihypertensive drugs and greater IVC diameter (a proxy for sub-clinical volume expansion)[22] were both independent determinants of inadequate BP control.[21] Compared to patients who were using just one antihypertensive medication, the odds of poor control of hypertension assessed by 44-hour ambulatory BP monitoring were 1.53 in those who used 2 drugs, 2.49 in those on 3 drugs, and 3.21 for 4 or more antihypertensive medications (p=0.02).

The longitudinal part of this study shedsome light on the question of whether formerly hypertensive dialysis patients controlled on medication continue to need these drugs. It followed 114 patients with adequate BP control (44-hour ambulatory BP <135/85 mmHg) who underwent gradual withdrawal of their antihypertensive medications over 3-6 weeks; 80% of these patients developed uncontrolled hypertension. The development of hypertension correlated with the number of anti-hypertensive drugs used and a greater IVC diameter suggesting sub-clinical volume expansion. Thus, more medications and greater volume expansion are independent determinants of developing uncontrolled hypertension after wash-out of pre-existing antihypertensive therapy.[21]

Pilot studies have tested newer technologies such as bioelectrical impendence analysis (BIA) or lung ultrasound as tools to guide the management of dry-weight. For example, Hur et al. [23] randomized 156 hemodialysis patients to BIA-guided management of dry-weight versus usual care. Over a 12-month-long follow-up, postdialysis weight was reduced by 0.5±2.4 kg in the BIA group and remained unchanged in the control group. Compared with usual care, BIA-guided management of dry-weight provoked an average reduction of 4.5/2.6 mmHg in predialysis BP and a reduction of 6.6/3.7 mmHg in postdialysis BP.[23] This BP-lowering effect was evident despite the fact that antihypertensive drug use was decreased from 23% to 11% of participants assigned to BIA-guided management of dry-weight.[23]

Similarly, in a sub-study of the ongoing LUST trial,[24] 71 hypertensive hemodialysis patients without clinically overt volume expansion were randomized to a lung ultrasound-guided management of dry-weight versus standard-of-care treatment for 8 weeks. An average reduction of 0.71 kg in postdialysis weight was observed in the lung ultrasound group, whereas dry-weight was increased by 0.51 kg in the control group.[24] Compared with standard-of-care treatment, lung ultrasound-guided volume management was accompanied by an average reduction of 5.9/3.3 mmHg in 48-hour intra- and interdialytic BP.[24]

The process of dry-weight probing based on clinical judgment in order to achieve a patient's dry-weight is challenging. Although intensified ultrafiltration increases the incidence of intradialytic hypotension, its well documented adverse cardiovascular effects found in patients prone to this complication of dialysis cannot necessarily be extrapolated to (and certainly doesn't have the benefits from) the use of dry-weight probing. In our experience, dry-weight probing is well tolerated and not accompanied by deterioration in any domain of health-related quality of life.[15]

We hope that implementation of BIA, lung ultrasound or other assistive technologies will aid in the detection of volume-responsive hypertension and eliminate any potential risks of dry-weight probing; whether this will prove to be the case is, so far, unproven. Larger randomized trials with "hard" clinical endpoints directly comparing a volume management strategy guided by assistive technologies versus dry-weight probing based on clinical judgment are warranted to fully elucidate this crucial issue In the meantime, based on evidence from DRIP,[15] we believe that a "volume-first" approach through dry-weight probing is a safe and effective strategy and represents our standard-of-care when managing hemodialysis hypertension.

Arterial stiffness

Arterial stiffness is an important cause of systolic hypertension in patients with end-stage kidney disease. Compared to the typical age-related arterial stiffening observed in patients with essential hypertension, in those with end-stage kidney disease, the arteriosclerotic process is accelerated.[25] Since aortic stiffness causes alterations in arterial cushioning function, isolated systolic hypertension ensues.[26] These functional alterations include the premature return of the reflected pulse wave from the periphery back to the ascending aorta during systole rather than diastole, resulting in augmentation of aortic systolic pressure and pulse pressure.[26] Apart from the augmented LV afterload and coronary hypoperfusion during diastole, reduction in stiffness gradient across the arterial tree mediates the greater downstream pulsatile energy transmission toward the periphery and promotes the microvascular damage.[27] On this basis, longitudinal studies have shown that aortic pulse wave velocity (PWV) — the “gold-standard” marker of arterial stiffness — is a strong and independent predictor of cardiovascular and all-cause mortality among patients on hemodialysis.[28,29]

The association of arterial stiffness with the patterns and rhythms of interdialytic BP was explored in a cross-sectional analysis of 11,833 BP measurements obtained from 125 long-term hemodialysis patients using the trended cosinor model.[30] Whereas interdialytic weight gain was associated with an increase in the interdialytic slope (i.e., rising interdialytic BP), arterial stiffness had a profound influence on the intercept component of ambulatory BP pattern. Each 1-log increment in aortic PWV was associated with 20.3 mmHg increase in systolic BP, 7.2 mmHg increase in diastolic BP, and 12.8 mmHg increase in pulse pressure.[30] Increasing arterial stiffness had minimal effect on the slope of BP change over the interdialytic interval. However, the circadian amplitude of systolic and pulse pressure variation was blunted with increasing aortic PWV.[30]

The notion that arterial stiffness is a determinant of the interdialytic ambulatory BP is further supported by a secondary analysis of the Hypertension in Hemodialysis treated with Atenolol or Lisinopril (HDPAL) trial.[31] In this trial, 200 hypertensive hemodialysis patients with echocardiographically documented LV hypertrophy were randomly assigned to an atenolol-based or a lisinopril-based antihypertensive regimen for 12 months.[32] The overall BP-lowering strategy in HDPAL included dietary sodium restriction, dry-weight adjustment and intensification of antihypertensive therapy; the aim of this combined therapy was to control monthly monitored home BP to levels <140/90 mmHg.[32]

Among 179 HDPAL participants with available arterial stiffness data at baseline, aortic PWV was directly associated with 44-hour systolic BP and pulse pressure and inversely with diastolic BP.[31] After adjustment for several cardiovascular risk factors, each 1-m/sec increment in aortic PWV was associated with 1.34 mmHg higher 44-hour systolic BP ($\beta = 1.34 \pm 0.46$, $P=0.004$) and 1.02 mmHg higher 44-hour pulse pressure ($\beta = 1.02 \pm 0.33$, $P=0.002$), whereas the association of aortic PWV with 44-hour diastolic BP did not remain significant.[31] Although aortic PWV was an independent determinant of ambulatory BP at baseline, it was not a predictor of the response of ambulatory BP to therapy over the course of the trial. In unadjusted analyses, treatment-induced reductions in 44-hour BP at 3, 6 and

12 months of follow-up were similar across tertiles of baseline aortic PWV. In mixed linear model analysis adjusted for several cardiovascular risk factors, baseline aortic PWV did not predict the treatment-induced change in either 44-hour systolic BP or diastolic BP, but did independently predict overall improvement in 44-hour pulse pressure.[31]

The relative importance of arterial stiffness and volume as predictors of the treatment-induced regression of LV hypertrophy was investigated in a subsequent post-hoc analysis of the HDPAL trial.[33] The change in LV mass index from baseline to 6 months was −26.2 g/m^2 (95% CI: −49.2, −3.3) and the change from baseline to 12 months was – 35.7 g/m^2 (95% CI: −63.7, −7.6), respectively.[33] Contrary to our original hypothesis that arterial stiffness and regression of LV hypertrophy would be interrelated, baseline aortic PWV was neither a determinant of LV mass index at baseline nor a predictor of treatment-induced reduction in LV mass index during 6 and 12 months of follow-up.

By contrast, volume overload emerged as an important predictor of regression of LV hypertrophy. In fact, regression of LV hypertrophy was predominantly mediated through a reduction in LV internal diameter, whereas LV wall thickness was not modified over the 12-month follow-up; this suggests volume as a mediator. Furthermore, adjusting the analysis for IVC diameter (a proxy for volume status)[22] or 44-hour systolic BP (a proxy for dry-weight achievement) mitigated the treatment-induced reduction in LV mass index.[33] This again suggests the importance of volume achievement in inducing regression of LVH in long-term hemodialysis patients.

Taking the above observations together, although aortic PWV is undoubtedly a major determinant of systolic hypertension among patients on hemodialysis, the severity of arterial stiffness does not make hypertension more difficult to control. Adequate management of dry-weight appears to be an effective strategy in order to improve BP control and delay the progression of hypertension-related target-organ damage regardless of the severity of arterial stiffness.

Erythropoietin-induced hypertension

New-onset hypertension or worsening of pre-existing hypertension is a well-recognized but frequently underreported complication of therapy with erythropoietin-stimulating-agents.[34] The magnitude and time course of the pressor effect induced by erythropoietin remains unclear due to absence of either home or ambulatory BP monitoring[35]. Observational studies are further limited because the magnitude of BP elevation induced by erythropoietin therapy may be blunted by modifications in background antihypertensive therapy and more aggressive adjustment of dry-weight.[36,37] It has to be noted, however, that erythropoietin use was is an independent determinant of the prevalence of hypertension diagnosed by ambulatory BP monitoring.[21] In other studies using ambulatory BP monitoring, erythropoietin use was associated with a non-dipping nocturnal BP pattern[38] and that the hypertensive response to erythropoietin was more common among hemodialysis patients with pre-existing hypertension[39,40] or a family history of hypertension.[41]

The mechanistic background of erythropoietin-induced hypertension is not yet fully clear, but preclinical studies suggest that the pressor effect of erythropoietin may be mediated through an imbalance in the vascular tone favoring net vasoconstriction.[34] Besides the up-regulation of prostanoids and endothelin-1 or inhibition of the nitric-oxide pathway, administration of erythropoietin is also associated with enhanced sensitivity to the vasoconstrictive action of catecholamines and angiotensin II and mitigation of hypoxia-inducible vasodilatation responses.[34,42–45]

Whether the pressor effect of erythropoietin is mediated through an increase in red blood cell mass and viscosity or this effect is independent from the level of hemoglobin is another area of uncertainty.[46] Preclinical studies suggest that hemoglobin may be increased by erythropoietin in the absence of a hypertensive response (by treating animals with erythropoietin binding protein) and that administration of erythropoietin in the setting of iron deficiency may induce hypertension without correcting anemia .[34,45]

Although the exact mechanisms remain to be elucidated, clinicians should take into consideration the contributing role of erythropoietin, particularly in younger hemodialysis patients with diastolic hypertension. Adjustments in erythropoietin dose, dry-weight and antihypertensive therapy may be required as therapeutic approaches to erythropoietin-induced hypertension.

Conclusions

Systolic hypertension, either alone or combined with diastolic hypertension, is the most common phenotype of BP elevation among patients on hemodialysis. Since uncontrolled BP among these patients is often a manifestation of volume overload, non-pharmacological approaches are more likely to be effective in improving BP control than pharmacological ones. When hypertension remains unresponsive despite the management of dry-weight, antihypertensive therapy is our second-line approach to control BP (Figure 1).

Arterial stiffness is another important determinant of systolic hypertension among patents on hemodialysis, but this factor is not easily modifiable. Based on evidence from the HDPAL trial, however, arterial stiffness does not make hypertension more resistant to therapy and is not predictor of the treatment-induced regression of LV hypertrophy. Although this evidence cannot prove direct cause-and-effect associations, a combined strategy of dietary sodium restriction, dry-weight adjustment and antihypertensive medication use guided by monthly monitored home BP recordings was effective in improving BP control in the HDPAL trial regardless of the severity of arterial stiffness. Other non-volume-dependent mechanisms such as therapy with erythropoietin-stimulating-agents should also be taken into consideration, particularly in younger patients with diastolic hypertension.

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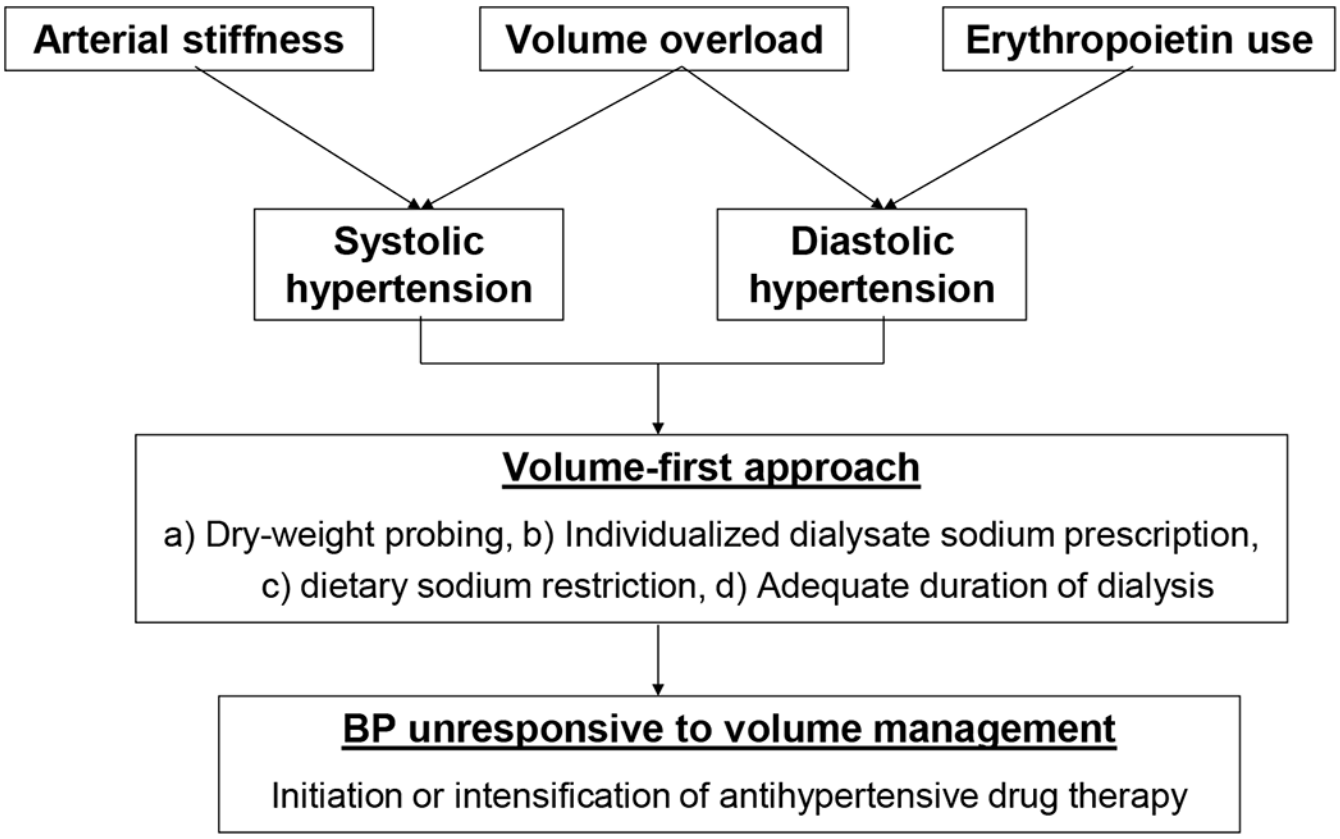

Figure 1:
Volume overload, arterial stiffness and erythropoietin use as causes of systolic versus diastolic hypertension among patients on hemodialysis.